

Human papillomavirus and gastrointestinal cancer: A review

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Abstract

Human papillomavirus (HPV) is one of the most common sexually transmitted infections worldwide. Exposure to HPV is very common, and an estimated 65%-100% of sexually active adults are exposed to HPV in their lifetime. The majority of HPV infections are asymptomatic, but there is a 10% chance that individuals will develop a persistent infection and have an increased risk of developing a carcinoma. The International Agency for Research on Cancer has found that the following cancer sites have a strong causal relationship with HPV: cervix uteri, penis, vulva, vagina, anus and oropharynx, including the base of the tongue and the tonsils. However, studies of the aetiological role of HPV in colorectal and esophageal malignancies have conflicting results. The aim of this review was to organize recent evidence and issues about the association between HPV infection and gastrointestinal tumours with a focus on esophageal, colorectal and anal cancers. The ultimate goal was to highlight possible implications for prognosis and prevention.

Key words: Human papillomavirus; Esophageal cancer; Colorectal cancer; Anal cancer; Oncogenesis; Prognosis; Prevention

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Core tip: Human papillomavirus is one of the major causes of infection-related cancer worldwide. Studies on the aetiological role of human papillomavirus (HPV) in colorectal and esophageal malignancies have yielded conflicting results. HPV status has emerged as a possible predictor of treatment response and long-term oncological outcomes for cancer sites where HPV-related and non-related cancers co-exist. Human papillomavirus vaccination is the key to improving HPV-related disease control, and universal vaccination could achieve optimal health benefits.

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INTRODUCTION

Human papillomaviruses (HPVs) are a large family of small double-stranded DNA viruses with established oncogenic potential, and they are recognized as a major cause of infection-related cancer worldwide (along with *Helicobacter pylori* and hepatitis viruses B and C). The International Agency for Research on Cancer (IARC) has found evidence of strong causal relationships between HPV and the following cancer sites: cervix uteri (ICD10-C53), penis (C60), vulva (C51), vagina (C52), anus (C21) and oropharynx, including the base of the tongue and the tonsils (C01, C09, C10)^[1]. Recent estimates have attributed approximately 4.8% (610000 cases) of all cancers worldwide to HPV infection^[2]. HPV could be responsible for some other cancers, including cancer of the esophagus, lip and oral cavity, but a causal role for HPV has not been established^[3]. Therefore, the figures reported above could underestimate the burden of cancer attributable to HPV.

Because the relationship of HPV infection and gastrointestinal carcinogenesis has implications for patient care and cancer prevention, we aimed to provide a review of the recent evidence in the field with a focus on gastrointestinal cancers.

HPV BIOLOGY AND ONCOGENESIS

HPV is a non-enveloped double-stranded DNA virus that infects basal keratinocytes in the skin or mucosal membranes.

HPV infection is almost exclusively acquired from sexual contact. The number of lifetime partners, early onset of sexually activity and co-infection with other sexually transmitted infection, including HIV, have been correlated with risk of HPV infection^[4-7].

Exposure to HPV is very common, and an estimated 65%-100% of sexually active adults are exposed to HPV at any anatomic site (oral, genital or anal) in their lifetime. The majority of HPV infections are asymptomatic, and 90% of persons exposed to HPV will clear the virus; the other 10% will have a persistent infection with an increased risk of developing carcinoma^[8,9].

HPV types are classified into "high-risk" and "low-risk" groups based on their oncogenesis potential (Table 1). High-risk HPV (hrHPV) types have the ability to cause human cancer. Currently, twelve types are designated by the IARC as carcinogenic, and eight additional types are designated as "probably" or

Table 1 Human papillomavirus classification

HPV group	Genotypes
High-risk types	
Carcinogenic	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59
Probably carcinogenic	68
Possibly carcinogenic	26, 53, 66, 67, 67, 70, 73, 82
Low-risk types	6, 11, 40, 42, 43, 44, 54, 61, 72, 81, 89

HPV: Human papillomaviruse.

"possibly" carcinogenic^[10]. HPV16 has been classified as "high risk" and is also the most prevalent hrHPV type in many regions of the world, followed by HPV18. Non-malignant diseases, such as genital warts, recurrent respiratory papillomatosis and oral papillomas, are attributable to low-risk HPV types, particularly HPV6 and 11^[11-16].

The HPV genome is organized into distinct control regions. The early region codes for viral non-structural proteins called E1, E2, E4, E5, E6 and E7. The late region codes for two capsid proteins for virion assembly called L1 and L2^[17].

HPV gene expression and the viral life cycle are tightly controlled by epithelial cell differentiation. The natural history of a high-risk HPV infection involves virus penetration in the basal layer through micro-abrasion and subsequent viral genome replication in basal epithelial cells when the virus is in its episomal form. The progression of a persistent infection is associated with HPV DNA integration into the host genome, and this step has been identified as critical for cancer promotion because it leads to the up-regulation of viral onco-protein expression, especially E6 and E7^[18-20]. The E6 and E7 proteins contribute to genetic instability through their inactivation of p53 and retinoblastoma protein (pRb). pRb is a negative regulator of the cyclin-dependent kinase inhibitor p16^{INK4a} (p16), and inactivation of pRb leads to up-regulation of p16^[21-23]. p16 is often used as a surrogate biomarker of HPV oncoprotein activity. Over 90% of HPV-positive oropharyngeal cancers overexpress p16, and immunohistochemical evidence of p16 overexpression has been widely used as a correlate for HPV oncogenic activity in cervical cancer and dysplasia^[24-26].

HPV infection causes cervical cancer and its precursor lesions at the squamocolumnar junction cells near the transformation zone. These cells appear to be multipotent residual embryonic cells, and an almost identical population was discovered at the gastro-esophageal squamocolumnar junction that was linked to Barrett's metaplasia^[27]. The anorectal junction is presumably another squamocolumnar junction similar to the cervix, but comparative microanatomy of the anal and cervical transition zones showed distinct topographical differences^[28]. This observation supports the discrepancy in the incidence of cervical and anal carcinoma. Indeed, although HPV DNA was detected at least as frequently in the anus as in the cervix, the

Table 2 Comparison of human papillomavirus detection methods

Methods	Specimens	Advantages	Disadvantages
Southern blotting assay	Fresh/frozen samples	High specificity, ability to differentiate between episomal and integrated DNA	Not easily applied to FFPE samples
ISH	FFPE, fresh samples	High specificity, ability to differentiate between episomal and integrated DNA	Low sensitivity, technically difficult
HPV PCR	Fresh/frozen samples brushing washing any body fluid	High sensitivity, cost effective	Low specificity, provides no quantitative measure of viral load, no confirmation of transcriptionally active virus
Real-time PCR	Fresh/frozen samples, FFPE brushing washing any body fluid	High sensitivity and specificity, ability to differentiate between episomal and integrated DNA	Labour-intensive
Reverse Transcriptase PCR	Fresh/frozen samples, FFPE	High sensitivity	Time consuming, technically difficult
p16 immunostaining	Fresh/frozen samples FFPE brushing washing	High sensitivity, easy and accessible to most laboratories, marker of transcriptionally active virus	Low specificity
Signal amplification methods	Fresh/frozen samples FFPE brushing washing	Easy to perform	False positive products, no typing

FFPE: Formalin-fixed, paraffin-embedded tissues; HPV: Human papillomavirus; PCR: Polymerase chain reaction; ISH: *In situ* hybridization.

cervical/anal cancer ratio is approximately 17:1^[3]. However, HPV infection alone is not sufficient to determine the carcinogenic potential of the lesion, and other cofactors are likely involved, including immune deficiency and host genetic factors. This prediction was confirmed indirectly by the fact that the majority of low-grade squamous intraepithelial lesions do not progress to high-grade lesions or carcinoma^[1,29-34].

HPV-related cancers in immunosuppressed patients

The incidence of HPV-related cancers is high in immunocompromised patients. HIV-infected patients show an increased risk of known HPV-related cancers, such as cervical and anal cancer. Moreover, the incidence of other possibly HPV-related cancers is increased in HIV-infected patients^[30].

Lifestyle and risk factors other than immune deficiency could be responsible for the heightened risk of several cancers in HIV patients^[31]. However, a similar pattern of incidence of HPV-related cancers emerged from studies of transplant patients^[32,33]. Transplant patients have generally different lifestyle exposures than HIV patients, but both groups have immune deficiency. Therefore, the immune deficiency is likely responsible for cancer progression and the high incidence of HPV-related cancers in HIV and transplant patients.

The risks of cancer of the penis, vulva, vagina, oral cavity, pharynx, esophagus, larynx and lip are increased in both transplant and HIV patients. The colorectal cancer risk is increased in transplant patients only.

HPV detection methods

Because HPV cannot be grown in conventional cell cultures, virus identification relies on molecular biology techniques.

Several methodologies are available for the detection

of HPV infection in tissue and exfoliated cell samples (Table 2). Despite the large number of studies, there is still controversy as to which method or combination of methods is best suited for HPV identification. Common methods include HPV detection by polymerase chain reaction (PCR), *in situ* hybridization (ISH) and the detection of p16 with immunohistochemistry (IHC).

The initial methods of HPV detection included radiolabelled nucleic acid hybridization assays, such as Southern blots and ISH. These methodologies generated high-quality information, but the disadvantages of these direct-probe approaches included low sensitivity, the need for relatively large amounts of purified DNA and time-consuming procedures^[35]. Mainstay HPV diagnostic methods involve signal amplification and PCR-based technologies. The PCR-based techniques are highly sensitive, specific and widely used^[36,37].

Several studies have also suggested that immunohistochemical detection of p16 overexpression may serve as a surrogate marker of functionally relevant HPV infection^[24-26]. It is a simple, fast and inexpensive procedure.

HPV AND ESOPHAGEAL CANCER

Esophageal cancer (EC) is the eighth most prevalent malignant tumour and the sixth leading cause of cancer mortality worldwide, with approximately 500000 new cases diagnosed and an estimated 406000 deaths each year^[38]. As reported above, the risk of esophageal cancer is increased in both HIV and transplant patients^[32].

The most common tumour type of esophageal cancer is squamous cell carcinoma (ESCC), followed by adenocarcinoma (EAC); there are significant epidemiological and aetiological differences between them. ESCC, which is more prevalent in Eastern countries and in developing countries, is the predominant subtype.

EAC, which is associated with Barrett's esophagus, is less common, but its incidence has been rising by 5%-10% each year, particularly in developed (Western) countries^[39]. Incidence rates of esophageal cancer vary greatly by geographic region. The highest ESCC rates occur in the "Asian Esophageal Cancer Belt", which extends from northern Iran east to China and north into Russia. The aetiology of EC remains poorly understood. A multifactorial aetiology may account for the great variability of EC incidence among different ethnic groups and geographic regions^[38,40]. Epidemiological studies suggest that tobacco smoking, heavy alcohol drinking, micronutrient deficiency^[2,41] and dietary carcinogen exposure may cause ESCC. Gastroesophageal reflux (GER) and Barrett's esophagus (BE) are the most important known risk factors for EAC^[42,43].

HPV and ESCC

The role of infection in the development of EC has long been suspected, and recent meta-analyses have assessed the incidence and aetiological role of HPV-ESCC tumour infection. Although HPV has been widely studied, the overall rate of HPV infection in ESCC remains controversial, and many studies have attempted to address this question. According to recent meta-analyses and reviews, worldwide HPV-ESCC infection rates range from 11.7% to 38.9%^[44-46]. Syrjänen *et al.*^[47] reported that the mean prevalence of HPV was 29.0% and ranged from 0% to 78%. Geographic origin was the strongest determinant for the observed disparities in infection rates. While low-incidence countries (*e.g.*, Australia and the United States) reported ESCC rates of approximately 2.5 per 100,000 people, the high-incidence countries, such as China and Iran, had rates as high as 250 per 100,000 people^[47-51]. This asymmetric geographic distribution remains largely unexplained. Several studies have correlated variability in HPV-ESCC infection rates with HPV detection methods. Many techniques were used to find evidence of the involvement of HPV in ESCC^[47,50]. To date, PCR and ISH are the most commonly used methods, and most studies use both techniques^[52-56]. The prevalence of overall HPV infection varies widely depending on detection method. Infection prevalence ranged from 17.6% for Southern blots to 32.2% for L1 serology, but the two most commonly-used methods demonstrated similar overall HPV-ESCC rates of 27.7% and 24.3%, respectively^[51]. In addition to these studies, several meta-analyses have demonstrated that detection method does not account for the variability in reported HPV-ESCC infection rates as variability persists within studies that use the same detection method^[47,51,57].

In 1982, Syrjänen *et al.*^[58] and Syrjänen^[59] first suggested the possibility that HPV might play an aetiological role in the progress of both benign and malignant squamous cell carcinoma of the esophagus. The well-known association between HPV and

oropharyngeal SCC and the histologic similarities between the oral squamous epithelium and upper esophagus could suggest a similar association. A wide range of studies on this topic have been conducted in various countries, including China, Korea, Iran, India, the United States and Australia^[60-62]. HPV16 and HPV18 are the most frequently detected types in HPV-associated cancers, and they are thought to be related to 70% of all cervical cancer cases. Yong *et al.*^[45] described a significant association between HPV16 and ESCC but not HPV18. In this meta-analysis, they reported an overall HPV16 prevalence rate of 11.7% vs 1.8% for HPV18. They also calculated separate ORs for HPV16 (OR = 3.55) and HPV18 (OR = 1.25), and HPV16 was the most frequently observed subtype in ESCC. This outcome agreed with other systematic reviews that showed HPV16 was the most commonly identified strain in HPV-ESCC infections using multiple methods. To date, however, studies examining the potential aetiological role of HPV infection in ESCC have been inconclusive.

Several studies of HPV infection in ESCC have shown little to no agreement between p16 overexpression and HPV-positivity. A recent systematic review suggested that p16 is not a reliable marker of HPV status in ESCC because the odds ratio of HPV-positivity in a p16-overexpressing ESCC lesion was 1.07 (95%CI: 0.70-1.62)^[63]. Recent meta-analyses have not evaluated p16 overexpression to characterize the potential aetiological role of HPV infection in ESCC. Studies examining both p16 overexpression and HPV positivity in ESCC have reported a low rate of double-positive ESCC lesions, approximately 5% of all cases^[64-71]. The available data are markedly different from oropharyngeal and cervical cancer data, and the association between p16 and HPV in ESCC therefore remains limited. Collectively, p16-overexpression and HPV serological data appear to indicate that, despite the reported rates of HPV infection in ESCC, HPV may not play a significant oncogenic role in ESCC. Nevertheless, a lack of correlation between p16-overexpression and HPV oncoactivity in ESCC would be unusual^[72]. This result was complicated by the geographic variation discussed previously because regions with the highest rates of ESCC also had the highest rates of HPV prevalence and HPV-ESCC infection. The geographic correlation between HPV and ESCC may suggest a causal link. However, this correlation must be considered with caution because studies from the same geographic areas report tremendous variability in HPV-ESCC infection rates^[66,73].

Therefore, the role of HPV in ESCC remains poorly defined. Geographic variability and methodological heterogeneity complicate the interpretation of current studies and lead to variable conclusions. HPV prevalence correlates strongly with high-ESCC-incidence regions, but in Western countries, such as

the United States, HPV-ESCC infection rates are low (on the order of 5%-15%). The p16 overexpression and HPV serological data do not currently support a definitive aetiological role for HPV in ESCC.

HPV and EAC

EAC is one of the fastest growing cancers in the Western world^[74]. GERD, BE, obesity, tobacco use and diet low in vegetables and fruit are the most important known risk factors for EAC^[42,43,75-80].

The analogue rise in head and neck cancers in Western countries has led to a suspicion that HPV may also play a role in EAC. Endoscopists and pathologists have often noted warty (papillomatous) lesions in the esophagus, which may indicate a viral infection^[81]. Herpes simplex virus, cytomegalovirus and Epstein-Barr virus have all been shown to infect the esophageal epithelium. Rajendra *et al*^[82] recently reported for the first time that transcriptionally active hr-HPV was strongly associated with Barrett's dysplasia (BD) and EAC, but HPV was biologically irrelevant in BE. This study was the first to find that HPV positivity, which was detected by PCR, was significantly higher in patients with BD and EAC compared to controls and individuals with Barrett's metaplasia. Even if this study did not prove causality, it suggested that HPV was associated with the transition from BE to dysplastic disease/adenocarcinoma. Biomarkers related to the transcriptional activity of hr-HPV have been investigated for the purpose of identifying the high-risk group of progressors to malignancy^[82-86]. When HPV DNA and markers of viral transcriptional activity, *i.e.*, p16 and E6/E7 mRNA, were all positive, there was a very strong association with disease severity along the Barrett's metaplasia-dysplasia-adenocarcinoma sequence compared to when the results for all markers were negative. Both an increasing hr-HPV viral load and integration into the host genome were significantly associated with disease severity in the Barrett's metaplasia-dysplasia-adenocarcinoma pathway. Another recent prospective study involving 40 patients reported that persistent biologically active hr-HPV infection (types 16 and 18) and p53 overexpression (assessed by immunohistochemistry and validated by DNA sequencing) were both independently associated with persistent dysplasia/neoplasia after endoscopic ablation of dysplastic BE/EAC^[87].

Recent findings from Antonsson *et al*^[88] showed the results of DNA quality testing (b-globin) through PCR and evaluation of the presence of HPV DNA in 241 histologically confirmed archived EAC and GEJAC (gastro-esophageal junction adenocarcinomas) tissue specimens from a population-based study in Australia. With a 97% DNA yield and acceptable quality in 233/241 specimens (201 EAC, 32 GEJAC), each sample was tested three times for HPV DNA. None of the 233 tumour specimens tested positive. There was no evidence of HPV DNA in esophageal adenocarcinoma tumour cells, and the researchers

strongly stated that: "HPV is unlikely to cause EAC or GEJAC". New studies could investigate persistent hr-HPV infection and p53 as potential dysplasia/EAC risk markers in clinical trials as well as in BE screening/surveillance studies.

Prognostic value of HPV status in esophageal cancer

Several authors have evaluated the prognostic significance of HPV-ESCC infection. In contrast to oropharyngeal lesions, for which several retrospective clinical studies have consistently proven that patients with HPV-positive head and neck squamous cell carcinoma have a better prognosis than patients with HPV-negative tumours^[89-92], the outcomes data for HPV in ESCC are still limited and conflicting. Furihata *et al*^[93] reported that high levels of p53 protein expression (probably due to p53 mutations) were inversely associated with HPV16 or 18 infection in esophageal cancers, and the prognoses of two groups, one with HPV16 or 18 infection and the other with p53 overexpression, were significantly poorer than the prognoses of the group with neither condition.

Hippeläinen *et al*^[94] reported that HPV was involved in 11% of 61 patients with ESCC but lacked prognostic value. Numerous authors have failed to show any significant association between HPV infection and patient survival^[95]. In contrast, a recent series of studies showed an improved overall and disease-free survival in ESCC patients with HPV-positive tumours. Cao *et al*^[96] reported that HPV-infected patients had better 5-year rates of overall survival (65.9% vs 43.4% among patients with HPV-negative tumours; $P = 0.002$ by the log-rank test) when HPV status was considered as an independent prognostic factor for overall survival (OS) and progression-free survival among patients with ESCC.

Because of this variability, clinical data do not suggest a prognostic role for HPV infection in ESCC, which precludes a definitive interpretation. Based on the evidence described above, it currently appears unlikely that HPV is clinically or aetiological relevant for ESCC. Thus, there is no evidence to recommend that ESCC patients should be tested for HPV infection outside of the context of a research study, and there is no clear indication to change clinical practice or treatment strategy for ESCC lesions based on HPV status. Nevertheless, Oei *et al*^[97] examined the response of HPV-positive cells to hyperthermia using cervical cancer cell lines infected with HPV 16 and 18, *in vivo* tumour models and *ex vivo*-treated patient biopsies. They found that hyperthermia at 42 °C for a duration of 60 min caused activation of the p53-dependent apoptotic pathway through degradation of E6. This outcome highlights the difference between HPV-negative and HPV-positive cells because the HPV-negative cells induced p53 and caused apoptosis after radiation alone, whereas HPV-positive cells required hyperthermia to promote these effects. Therefore, this finding may lead to further clinical studies of

hyperthermia with other HPV-associated cancers.

HPV AND COLORECTAL CANCER

Colorectal cancer (CRC) is the third most common cancer in men and the second most common in women worldwide. There is a wide geographical variation in incidence across the world, with the highest estimated rates in Australia/New Zealand (ASR 44.8 and 32.2 per 100000 in men and women, respectively) and the lowest in Western Africa (4.5 and 3.8 per 100000 in men and women, respectively)^[98]. Although hereditary forms of CRC have been well established, most cases are sporadic^[99]. Several epidemiological studies have shown that factors related to lifestyle can contribute to the occurrence of CRC, such as high consumption of red meat or tobacco smoking^[100]. However, the role played by environmental factors in the pathogenesis of this malignancy is still under investigation. Due to the vast microbial population in the human intestine and the identification of infectious agents as risk factors for different types of cancers, researchers around the world have recently assessed the relationship between various infectious pathogens and the onset of colorectal neoplasia^[101].

HPV could potentially infect the colorectum by an ascending infection from anogenital sites or thorough haematogen or lymphogen spread, and HPV has been hypothesized to be a potential aetiological factor associated with colorectal cancer^[102-106].

In recent years, a growing number of studies has investigated the presence of HPV in colonic tissues. The majority of the authors found a much higher prevalence of HPV DNA in malignant tissues compared to controls (disease-free patients or adjacent colic mucosae), which suggested a potential role for HPV infection in colorectal carcinogenesis^[107], but the association between HPV and colorectal cancer remains controversial and inconclusive.

There is wide variation in the reported prevalence in the literature, due partly to heterogeneity in HPV detection methods. Although the HPV prevalence was higher in PCR-based than in non-PCR-based studies, there was substantial heterogeneity even between studies using the same PCR-based method. In addition, storage of the specimens might have interfered with virus detection. In fact, viral prevalence tends to be higher in studies in which fresh or frozen tissue samples were analysed than in studies using formalin-fixed and paraffin-embedded tissue^[108].

The HPV detection rate in colorectal cancer ranged from 0% to 84%^[107-109]. The overall prevalence of HPV was highest in publications from South America, Asia and the Middle East, with ranges from 32% to 45%, whereas the prevalence was 3% or less in studies from North America, Europe and Australia, which was similar to variations in HPV prevalence observed for other non-cervical cancers^[108,110-113]. Interestingly, this geographical variation in HPV prevalence in colorectal cancer

appeared to be the opposite of the global pattern of colorectal cancer incidence and could reflect differences in HPV prevalence across the region. Furthermore, some populations may be more susceptible than others to HPV-associated colorectal carcinomas. Whereas HPV18 was more frequently detected in colorectal cancer cases from Asia and Europe, HPV16 was more prevalent in colorectal cancer cases from South America^[108].

Moreover, Burnett-Hartman^[114] analysed the correlation between HPV and colorectal cancer using the Hill criteria^[115]. As stated by the author, there was some evidence for analogy, biological plausibility and strength of association but only weak evidence for consistency, specificity and coherence. Thus far, temporality, biological gradient and experimentation have not been evaluated in published studies.

Demonstrating the integration of HPV in the host genome and the expression of viral oncogenes is also important. Lorenzon *et al.*^[116] investigated the integration status of HPV16 in colorectal tumours by detecting the virus exclusively in its episomal form, in barely traceable quantities and when it was transcriptionally inactive. Previously, Bodaghi *et al.*^[117] examined 31 of the HPV16 DNA-positive samples for the intact HPV16 E2 gene and frequently found viral integrated DNA in the tumour tissue.

Although two recent meta-analyses have demonstrated a significant increase in colorectal cancer risk associated with the presence of the virus^[108,109], the published literature does not provide convincing evidence for a strong association. The sample size in each of the studies was small, and genotyping methods varied across studies. However, because the pathogenesis of colorectal cancer is multifactorial, HPV may play a role in a subset of cancers. Additional large-scale multicentre studies using standardized methodologies and researchers investigating the viral genome integration as well as the molecular basis of HPV-related carcinogenesis are needed to better understand the possible role of HPV in colorectal cancer.

HPV AND ANAL CANCER

Anal cancer commonly occurs in the transformation zone between the squamous and columnar epithelium of the anal canal. Squamous cell carcinoma (SCC) is the most common histological type and accounts for 85% of all anal cancers^[118]. SCC is closely related to persistent infection with human papilloma virus. Indeed, HPV is detected in 80%-90% of anal cancers, and HPV16 is the predominant type identified in approximately 80% of patients^[119,120] with a frequency much higher than that in other anatomic sites^[120-125]. This frequency possibly reflects a differential tropism of HPV 16 or an increased probability of HPV 16 to lead to malignant transformation in the anal mucosa. HPV prevalence in anal cancer varies by geographic region, with the highest prevalence in North America and Europe and the lowest in Africa^[119].

Similar to cervical cancer, squamous cell carcinoma of the anus is preceded by a spectrum of precursor lesions of varying cytological and histological severity that are defined as anal intraepithelial neoplasia (AIN). Grades 2 and 3 are grouped together as high-grade anal intraepithelial neoplasia (HGAIN) and are associated with a higher risk of invasive cancer. The natural history of AIN is not well understood. However, it is believed that low-grade AIN may undergo spontaneous regression or progress to high-grade AIN, which is similar to cervical cancer. The rate of progression from anal HGAIN to invasive cancer is unknown but is estimated to be notably lower than the risk of progression to cancer for cervical high-grade squamous intraepithelial lesions (approximately 1 to 80 per year)^[126-128]. AIN2/3 is related to HPV in more than 90% of cases, particularly with serotype 16^[119,120].

Anal cancer accounts for approximately 2%-3% of gastrointestinal tract malignancies, with 27000 new cases diagnosed worldwide in 2008 and age-adjusted incidence rates approximately 1 per 100000 people^[2,119]. Anal cancer is a disease of older individuals, with a peak in those aged 55 to 64 years, and the median age for diagnosis is 60 years. In most countries, women are more commonly affected than men^[129].

Although anal cancer is relatively rare, the incidence has been increasing over the past decade in different countries in both sexes^[130]. In the United States, the incidence of anal cancer has more than doubled since 1975 and continues to rise by approximately 2.2% per year for both genders^[131]. In Denmark, the incidence increased by 2-fold in both women and men in the 30-year period between 1978 and 2008, and the incidence of AIN increased by 1.3-fold in the shorter observation period between 1998 and 2008^[132]. Similar patterns have been observed in other European countries and in Australia^[130,133]. The reason for the increasing incidence of anal cancer is not well understood but may reflect changes in sexual behaviour, such as the increased adoption of high-risk sexual activities, including receptive anal intercourse and increased sexual promiscuity^[134]. Furthermore, most of this increase is attributed to a certain at-risk population, specifically men who have sex with men (MSM)^[135] and HIV-positive individuals^[118,136] that have a significantly higher risk of anal cancer compared to the general population. MSM are nearly 20 times more likely than heterosexual men to develop the disease^[129], and there is a 10-fold increase in incidence in HIV-positive women compared to HIV-negative women^[131]. There was also an increase of more than 40-fold in men with HIV infection who only have sex with women compared to their HIV-uninfected counterparts, and the increase was even higher among HIV-positive MSM^[137,138]. The risk of SCC increases with the duration of HIV infection, and it is not reduced to the use of highly active antiretroviral therapy (HAART)^[30,139]. Women with a history of HPV-associated genital (*i.e.*, vulval, vaginal or cervical) high-grade squamous intraepithelial lesions or cancer^[140] and

people with immune deficiency also have a high risk for this disease^[141].

In HIV-infected men who have sex with men, hrHPV is detected in approximately 74% of individuals, and concurrent infections with several HPV types are also common^[128,142]. Furthermore, studies have demonstrated that the prevalence of HPV infection of the anal region is common in both heterosexual man and HIV-uninfected individuals. In a study in immunocompetent asymptomatic heterosexual men, the prevalence of overall anogenital HPV infections was 24.8% and, of the men with anal HPV infection, 33.3% had an oncogenic HPV type^[143]. In HIV-negative women with no history of HPV-related pathology of the vulva, vagina and cervix, the prevalence of anal HPV varied from 4% to 22% and rose to 23%-36% in women with known HPV-related pathology. In HIV-positive women, the prevalence of HPV in the anus varied from 16% to 85% and was higher than the prevalence in the cervix in the majority of studies^[144].

A recent study focusing on the natural history of anal HPV infection in heterosexual women showed that approximately 85% of women cleared low risk-types and non-16 hr-HPV infections within three years, whereas only 76.2% of women cleared HPV16 infections. The slower rate noted for HPV16 in the anus was not surprising because HPV16 appears to be more important than the other hr-HPV types in anal cancer. Interestingly, one of the strongest predictors of anal HPV16 persistence was having a concomitant cervical infection with HPV16. Anal sex behaviours, including anal intercourse, anal touching and lack of condom use during anal sex, were also associated with HPV16 persistence^[145].

Several case-control studies have assessed the risk of anal cancer associated with HPV infection and reported odds ratios between 2 and 7 for HPV 16 and HPV 18 seropositivity for both men and women^[119].

Anal intercourse is probably the most efficient way of acquiring anal HPV infections, but it is not the only mode of transmission for HPV to the anal canal. Several studies have found anal HPV in women with no history of anal receptive intercourse. Furthermore, most publications have found that HPV infection of the cervix is a significant risk factor for anal HPV^[145,146]. In addition, studies have shown a high degree of genotype-specific concordance among women with concurrent anal and cervical infections, which is consistent with a common source of infections or spread from one site to the other^[147]. The plausibility that the cervix acts as a source for anal HPV infection is enhanced by the anatomic proximity of the vaginal introitus to the anus, and the likelihood that anal infection acts as a source for cervical infection is somewhat less probable. Several studies have found the same HPV type on the hands or fingertips as in the genital area in men and in women^[148-150]. Although HPV on the fingers likely represents DNA deposits from the genitals rather than a true infection, the possibi-

lity of infection through autoinoculation *via* vaginal secretions, digital or fomite transference cannot be excluded^[151].

Anal cancer screening

Screening for anal cancer is currently being considered for high risk groups (*e.g.*, HIV-infected men having sex with men). Screening should involve the assessment of anal cytology obtained with a swab and subsequent study with high-resolution anoscopy (HRA) when cytological abnormalities are detected. The sensitivity of a single anal cytology test for detecting histological HSIL (AIN2/3) ranges from 55% to 93%, and the specificity ranges between 32% and 81%^[129]. Many studies have found poor correlation between the grade of the cytology report and the grade diagnosed on a subsequent biopsy^[152]. Moreover, sensitivity decreases in the highest risk group^[129]. For these reasons and given the low specificity of anal cytology as a screening tool, some clinicians have proposed that patients should be referred immediately for an HRA. Additionally, using HPV testing could help reduce the need for HRA. However, HPV testing can have a low specificity for anal HSIL because HIV-infected patients have a high HPV prevalence, and multiple HPV types may be detected in the anal canal.

Although there is currently no evidence of its efficacy, some authors have recommended screening high-risk HIV-positive individuals^[152,153], such as MSM, those with a history of condylomata and women with cervical or vulvar dysplasia. This recommendation is based on indirect evidence taken from various epidemiological studies that highlight the high incidence of anal cancer among these subgroups, the availability of the test, the morbidity and mortality associated with anal cancer and studies evaluating the cost-effectiveness of the screening strategy.

Prognostic value of HPV status in anal cancer

Although anal cancer chemoradiotherapy (CRT) has become the standard treatment for patients with locoregional disease, there has been little improvement in survival over the last few decades^[154]. Therefore, there is growing interest in the determination of molecular tumour factors that may predict either a response or resistance to standard CRT.

Recently, in HPV-associated malignancies, particularly oropharyngeal head and neck SCC, most studies have revealed a more favourable prognosis in patients with an HPV-positive tumour compared to HPV-negative patients. Moreover, recent data indicate that treatment response to radiotherapy (RT) or chemoradiotherapy (CRT) is superior for HPV-positive tumours compared to HPV-negative tumours^[155]. In patients with cervical cancer, Kim *et al.*^[156] recently reported that the HPV DNA load was a strong independent prognostic factor for disease-free survival after radical RT. However, the biological basis for this

improved outcome in HPV-positive cases was not clear.

However, because the detection rate of HPV DNA in anal SCC commonly exceeds 90%, a comparison between only HPV-positive and HPV-negative cancers with respect to treatment response and long-term outcome is very difficult.

The recent understanding of HPV infection as a causative factor in treatment response and prognosis further encouraged investigators to examine surrogate markers for HPV infection. Among these factors, the cell cycle regulatory protein p16^{INK4a} (p16) has emerged as the best candidate due to its association with high-risk HPV infection. This cyclin-dependent kinase inhibitor is normally repressed by a phospho-retinoblastoma protein (pRB)/transcription factor E2F complex, but this suppression is inhibited by the high-risk HPV oncoprotein E7, which results in overexpression of p16. In line with that finding, several studies have indicated that p16 detection by IHC is predictive for a significantly improved response to treatment with RT/CRT and a more favourable prognosis in patients with HPV-associated malignancies^[157].

Serup-Hansen *et al.*^[158] found that p16 positivity was a strong independent prognostic factor for improved overall survival (OS) and disease-specific survival (DSS) in patients with anal carcinoma. Rödel *et al.*^[157] showed that a high HPV16 DNA load was an independent prognostic factor associated with improved locoregional tumour control and overall survival, and they also revealed increased locoregional control in patients with a high p16 labelling score compared to patients with low p16 expression. Another recent retrospective study provided an evaluation of the prognostic importance of local control and survival of various combinations of HPV/p16 status in a total of 106 patients treated with CRT. Mai *et al.*^[159] concluded that p16 positivity alone was not a sufficient marker for HPV-induced transformation because p16 positivity can be caused by an event other than HPV transformation, and that outcome conferred a significantly different prognosis. HPV+/p16+ status only reliably identified HPV-transformed tumours with an extremely favourable prognosis. Tumours with p16 overexpression without HPV infection seemed to have a particularly unfavourable prognosis and may therefore require more treatment to improve results.

However, other studies were unable to find an association between p16 expression and outcomes using conventional IHC staining status^[160]. This result may be related to the fact that most of the cases were HPV-positive according to all testing techniques, which made any subset analysis of the IHC score very difficult. Differences in scoring and definition of p16 positivity, the retrospective study design and smaller sample sizes may also explain the discordant results. Therefore, these data need to be validated prospectively in a larger patient cohort. Additionally, the molecular background of tumours that are p16+

without HPV infection has to be investigated further.

HPV VACCINATION IS THE KEY TO IMPROVING HPV-RELATED DISEASE CONTROL

Cervical cancer screening, along with primary prevention measures to control sexually transmitted diseases, has long been the main intervention to reduce the burden of HPV-related disease^[161].

With an improved understanding of the role of HPV infection in several malignancies, vaccination has emerged as a central tool for preventing HPV-related disease.

Currently, three vaccines against HPV are approved. The bivalent vaccine (HPV2) is designed to prevent infection from HPV types 16 and 18, and the quadrivalent vaccine (HPV4) is active against HPV types 6, 11, 16 and 18. Data from clinical trials have shown that both vaccines can prevent premalignant genital (cervical, vulvar and vaginal) and anal lesions in females from 9 to 26 years of age. The quadrivalent vaccine was also effective in males ages 9 to 26 for the prevention of genital warts, penile intraepithelial neoplasia and AIN. Although no data from clinical trials are currently available to demonstrate efficacy for the prevention of oropharyngeal cancer, the HPV vaccine is likely to offer protection against these cancers as well because most cases can be attributed to HPV16. Furthermore, clinical trials recently established the safety, efficacy and immunogenicity of the nonavalent vaccine, which includes the next five most commonly detected oncogenic types in HPV-associated cancers (*i.e.*, types 31, 33, 45, 52 and 58)^[16,162,163].

By the beginning of 2007, routine vaccination programmes against HPV were implemented in the majority of Western countries. However, the high cost of the vaccine, the diffusion of movements against vaccine use and difficulties in reaching the adolescent population that is the target of vaccination have hindered widespread coverage^[164].

Moreover, most existing vaccination programmes target pre-adolescent girls only through school-based or health centres, and these programmes often include catch-up programmes for older girls and women. Therefore, most countries do not currently include boys in HPV vaccination programmes.

Studies comparing the incremental benefits of vaccinating males and females to female-only immunization indicate that gender-neutral vaccination programmes are likely to further reduce the incidence of HPV-related disease in both sexes. Instead, cost-effectiveness analyses indicate that including males in current HPV vaccination programmes may not be cost-effective if high coverage of females is achieved^[165-169]. However, in many countries, the goal of vaccination coverage > 80% among females has not been reached.

Failure to achieve high population coverage hampers the additional protection associated with herd immunity such that the potential benefits of vaccination are not fully realized. For instance, significant reductions in HPV infections and genital warts in girls and boys younger than 20 years of age were observed only where high coverage target was reached^[170].

In many developed countries, the burden of HPV-associated cancers in men is comparable to the burden in women. In Europe, approximately 30% of all HPV-related cancers are estimated to occur in males^[171]. Moreover, men having sex with men receive little benefit from strategies based on the vaccination of women only.

The results of economic analyses have limitations. They critically depend on a modelling approach and assumptions about natural immunity, vaccination strategies, vaccine coverage rate and HPV-related diseases. Furthermore, these studies do not consider the epidemiological trend of HPV-related diseases, such as the observed increase in the incidence of anal and head and neck cancers^[172]. Moreover, published cost-effectiveness studies have been criticized for underestimating the benefits of universal vaccination related to several non-health factors, including economic benefits, such as improved patient, family and career productivity. The assessment of the cost-effectiveness of universal HPV vaccination also depends on the estimated costs of vaccination. Strategies to reduce the cost associated with vaccination could make universal vaccination cost-effective. For instance, ongoing studies are exploring the change from a three-dose schedule of HPV vaccination to a two-dose schedule^[173,174].

To increase the impact of HPV vaccination, Australia has been the first country to offer free HPV vaccines for boys as well as girls. Canada and the United States now also recommend vaccinating boys. Austria recently became the first European Union country to offer universal HPV vaccination.

Finally, it must be emphasized that the potential population level impact of current prophylactic HPV vaccination on cancers other than cervical cancer is particularly important because there are very few effective screening programmes for most of these malignancies.

Modelling analyses suggest that HPV vaccination can substantially reduce the burden of HPV-associated diseases, with approximately 30%-40% of health gains deriving from the prevention of non-cervical cancers^[163].

Optimal implementation of HPV vaccines is an important public health challenge. Targeted efforts are needed to increase vaccine uptake among girls, and universal vaccination should be carefully considered^[174]. Indeed, the extension of vaccination to boys is highly desirable and should be implemented in many countries in the next few years.

CONCLUSION

Human papillomavirus is one of the major causes of infection-related cancer worldwide. A clear association has already been established between HPV and genital malignancies, anal and oropharyngeal cancers. Although there is ongoing investigation into the potential aetiological role of HPV in the development of esophageal and other cancers, most studies to date have been inconclusive.

Identification of HPV-related cancers is clinically relevant because HPV status is emerging as a possible predictor of treatment response and long-term oncological outcomes that might help identify patients who are candidates for different treatment regimens.

Further research is required to improve our understanding of the natural history of HPV infection, its oncogenesis and the potential clinical implications. Screening could be introduced to decrease incidence of anal cancer in high-risk groups. Nevertheless, vaccination represents the best available strategy to reduce the burden of HPV-related cancers.

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